The science behind Immuno-Oncology is based upon the understanding of the mechanisms tumours use to escape the immune system and how these can be modulated to promote tumour destruction. At Bristol-Myers Squibb, we are committed to furthering the science and understanding of Immuno-Oncology through our research and development, as well as by supporting educational activities.

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ABSTRACT BOOK
Methods: We utilized our recently established in vivo xenograft model of BM-disseminated human myeloma (using engineered CXC4R4-expressing RPMI8226 cells), as well as analysis of MM cell lines, stromal components and primary samples from patients (pts) with MM.

Results: Evaluation of the cytokines in sera of MM-inoculated mice in comparison to control mice detected increased levels of the CXCL13 chemokine being the highest factor among the broad panel analyzed. Elevated mCXCL13 was also detected in bone marrow (BM) samples from the MM-bearing mice, and correlated with induced expression of murine factors associated with osteoclast (OC) activation and osteoclastogenesis (RANKL, TNF, GPNMB, CT5K, DSCAR). IHC analyses of MM-occupied murine BM revealed myeloid cells being the main source of increased mCXCL13, while human RPMI8226 cells in murine BM milieu also expressed detectable levels of hCXCL13. In addition, hCXCL13 mRNA was found to be expressed by MM cell lines (n=8), BM stromal cell lines and peripheral-blood generated Mφ. Strong induction of CXCL13 expression in both MM and stromal cells was detect- ed upon their co-culture. Furthermore, CXCL13 expression in BMSCs and Mφ was significantly induced following RANKL treatment; in turn, addition of CXCL13 up-regulated RANKL levels, demonstrating a positive regulation loop between CXCL13 and RANKL. Functional tests revealed the ability of CXCL13 to induce in vitro formation of TRAP+ OCs, while CXCL13 neutralizing antibodies blocked this effect. Furthermore, CXCL13 neutralization markedly decreased RANKL expression in BMSCs. Of note, CXCR5, cognate CXCL13 receptor, was expressed predominantly by stromal and myeloid cells, suggesting the paracrine effects of MM-generated CXCL13. Mechanically, we found that TGFβ signaling was involved in CXCL13 induction in both MM and stromal cells. Addition of TGFβ receptor kinase SB-431542 interfered with the activation triggered by the interaction between MM cells and stromal components and prevented the increase in CXCL13 expression. Finally, we evaluated the presence of hCXCL13 in primary MM samples. CXCL13 transcript was detected in BM aspirates from MM pts (n=20), its expression was significantly upregulated upon co-culture with primary MM samples. CXCL13 up-regulation of murine factors associated with osteoclast (OC) acti-vation and osteoclastogenesis (RANKL, TNF, GPNMB, CT5K, DSCAR). IHC analyses of MM-occupied murine BM revealed myeloid cells being the main source of increased mCXCL13, while human RPMI8226 cells in murine BM milieu also expressed detectable levels of hCXCL13. In addition, hCXCL13 mRNA was found to be expressed by MM cell lines (n=8), BM stromal cell lines and peripheral-blood generated Mφ. Strong induction of CXCL13 expression in both MM and stromal cells was detected upon their co-culture. Furthermore, CXCL13 expression in BMSCs and Mφ was significantly induced following RANKL treatment; in turn, addition of CXCL13 up-regulated RANKL levels, demonstrating a positive regulation loop between CXCL13 and RANKL. 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In addition, plasma level of CXCL13 was significantly higher in MM pts (n=44) (148 pg/ml±138) in comparison to normal individuals (n=9) (19 pg/ml±7.6). Formation of TRAP+ OCs, while CXCL13 neutralizing antibodies blocked this effect. Furthermore, CXCL13 neutralization markedly decreased RANKL expression in BMSCs. Of note, CXCR5, cognate CXCL13 receptor, was expressed predominantly by stromal and myeloid cells, suggesting the paracrine effects of MM-generated CXCL13. Mechanically, we found that TGFβ signaling was involved in CXCL13 induction in both MM and stromal cells. Addition of TGFβ receptor kinase SB-431542 interfered with the activation triggered by the interaction between MM cells and stromal components and prevented the increase in CXCL13 expression. Finally, we evaluated the presence of hCXCL13 in primary MM samples. 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Summary/Conclusions: Altogether, our data define a previously unrecognized role of CXCL13 in MM, unravel its involvement in the osteoclastogenic process and suggest CXCL13 as potential novel target for the diagnosis and treatment of MM.

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MESENCHYMAL STEM CELLS (MSC) PROMOTES TUMOR MICROENVIRONMENT TRANSFORMATION DRIVING GRANULOCYTE-LIKE MYELOID DERIVED SUPPRESSOR CELLS (G-MDSC) ACTIVATION IN SMOLDERING AND MULTIPLE MYELOMA PATIENTS

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Background: A well-recognized feature of multiple myeloma (MM) is the inti-